

Title (en)  
METHODS OF ALTERING GENE EXPRESSION BY PERTURBING TRANSCRIPTION FACTOR MULTIMERS THAT STRUCTURE REGULATORY LOOPS

Title (de)  
VERFAHREN ZUR VERÄNDERUNG DER GENEXPRESSION DURCH STÖREN VON TRANSKRIPTIONSAKTOR-MULTIMEREN, DIE REGULATORISCHE SCHLEIFEN STRUKTURIEREN

Title (fr)  
PROCÉDÉS DE MODIFICATION DE L'EXPRESSION GÉNÉRIQUE PAR PERTURBATION DE MULTIMÈRES DU FACTEUR DE TRANSCRIPTION QUI STRUCTURENT LES BOUCLES RÉGULATRICES

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Application  
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Abstract (en)  
The invention relates to methods of modulating the expression of one or more genes in a cell by modulating the multimerization of a transcription factor and/or modulating the formation of enhancer-promoter DNA loops, and thereby modulating the expression of the one or more genes. The invention also relates to treating diseases and conditions involving aberrant gene expression by modulating the multimerization of a transcription factor and/or modulating the formation of enhancer-promoter DNA loops. The invention also relates to methods for screening for compounds that modulate expression of one or more genes in a cell.

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Citation (applicant)  

- US 2016059399 W 20161028
- US 2016237490 A1 20160818 - HNISZ DENES [US], et al
- US 2010144031 A1 20100610 - JAENISCH RUDOLF [US], et al
- US 2011076678 A1 20110331 - JAENISCH RUDOLF [US], et al
- US 2011088107 A1 20110414 - HANNA YAQUB [US], et al
- US 2012028821 A1 20120202 - JAENISCH RUDOLF [US], et al
- US 201662377520 P 20160819
- US 2017047674 W 20170818
- US 2016319260 A1 20161103 - JOUNG J KEITH [US], et al
- US 2016208243 A1 20160721 - ZHANG FENG [US], et al
- US 2012046346 A1 20120223 - ROSSI DERRICK [US], et al
- US 2011032679 W 20110415
- WO 2011130624 A2 20111020 - IMMUNE DISEASE INST INC [US], et al
- US 2011046861 W 20110805
- US 2011054636 W 20111003
- US 2011054617 W 20111003
- US 201314390100 A 20130309
- US 2014068797 A1 20140306 - DOUDNA JENNIFER A [US], et al
- US 2014186919 A1 20140703 - ZHANG FENG [US], et al
- US 2014170753 A1 20140619 - ZHANG FENG [US]
- US 2014034387 W 20140416
- WO 2014172470 A2 20141023 - WHITEHEAD BIOMEDICAL INST [US]
- US 5998203 A 19991207 - MATULIC-ADAMIC JASENKA [US], et al
- US 2014206753 A1 20140724 - GUILD BRAYDON CHARLES [US], et al
- WO 2010053572 A2 20100514 - MASSACHUSETTS INST TECHNOLOGY [US], et al
- US 201261617468 P 20120329
- US 4897355 A 19900130 - EPPSTEIN DEBORAH A [US], et al
- US 5171678 A 19921215 - BEHR JEAN-PAUL [FR], et al
- US 5334761 A 19940802 - GEBEYEHU GULILAT [US], et al
- WO 2010042877 A1 20100415 - TEKMIRA PHARMACEUTICALS CORP [CA], et al
- WO 2005121348 A1 20051222 - PROTIVA BIOTHERAPEUTICS INC [CA], et al
- US 5744335 A 19980428 - WOLFF JON A [US], et al
- US 2014288160 A1 20140925 - GUILD BRAYDON CHARLES [US], et al
- US 5885613 A 19990323 - HOLLAND JOHN W [AU], et al
- US 4737323 A 19880412 - MARTIN FRANCIS J [US], et al
- US 83528197 A 19970410
- US 60083294 P
- EP 0321201 A2 19890621 - COMMW SCIENT IND RES ORG [AU]
- US 5211657 A 19930518 - YAMADA YOSHIHIKO [US], et al
- "Current Protocols in Protein Science, and Current Protocols in Cell Biology", December 2008, JOHN WILEY & SONS, article "Current Protocols in Molecular Biology, Current Protocols in Immunology"
- ELBASHIR ET AL., NATURE, vol. 411, 2001, pages 494 - 498

- HASELOFF ET AL., NATURE, vol. 334, 1988, pages 585 - 591
- HEYES, J. ET AL., J CONTROLLED RELEASE, vol. 107, 2005, pages 276 - 287
- MCINTYRE GFANNING G: "Design and cloning strategies for constructing shRNA expression vectors", BMC BIOTECHNOL., vol. 6, 2006, pages 1, XP021005991, DOI: 10.1186/1472-6750-6-1
- MCKUSICK, V.A.: "A Catalog of Human Genes and Genetic Disorders", 1998, JOHNS HOPKINS UNIVERSITY PRESS, article "Mendelian Inheritance in Man"
- "National Center for Biotechnology Information", 1 May 2010, NATIONAL LIBRARY OF MEDICINE
- ONLINE MENDELIAN INHERITANCE IN ANIMALS (OMIA)
- HNISZ ET AL.: "Insulated Neighborhoods: Structural and Functional Units of Mammalian Gene Control", CELL, vol. 167, no. 5, 17 November 2016 (2016-11-17), pages 1188 - 1200, XP029812213, DOI: 10.1016/j.cell.2016.10.024
- CREYGHTON ET AL.: "Histone H3K27ac separates active from poised enhancers and predicts developmental state", PROC NATL ACAD SCI USA, vol. 107, 2010, pages 21931 - 21936, XP055074651, DOI: 10.1073/pnas.1016071107
- RADA-IGLESIAS ET AL.: "A unique chromatin signature uncovers early developmental enhancers in humans", NATURE, vol. 470, pages 279 - 283, XP055308006, DOI: 10.1038/nature09692
- ZHANG, Y ET AL.: "Model-based Analysis of ChIP-Seq (MACS", GENOME BIOL., vol. 9, 2008, pages R137, XP021046980, DOI: 10.1186/gb-2008-9-9-r137
- LIU ET AL.: "Editing DNA methylation in the mammalian genome", CELL, vol. 167, no. 1, pages 233 - 247
- TSAI, QS ET AL., NAT BIOTECHNOL., vol. 32, no. 6, 2014, pages 569 - 576
- PHILLIPS-CREMINS, J.E.SAURIA, M.E.G.SANYAL, A.GERASIMOVA, T.I.LAJOE, B.R.BELL, J. S.K.ONG, C.-T.HOOKWAY, T. AGUO, C.SUN, Y. ET AL.: "Architectural protein subclasses shape 3D organization of genomes during lineage commitment", CELL, vol. 153, 2013, pages 1281 - 1295
- KLEINSTIVER ET AL.: "High-fidelity CRISPR-Cas9 nucleases with no detectable genome-wide off-target effects", NATURE, vol. 529, pages 490 - 495, XP055650074, DOI: 10.1038/nature16526
- YANG ET AL.: "PAM-Dependent Target DNA Recognition and Cleavage by C2c1 CRISPR-Cas Endonuclease", CELL, vol. 167, 2016, pages 1814 - 1828
- ZETSCHKE B ET AL.: "Cpf1 is a single RNA-guided endonuclease of a class 2 CRISPR-Cas system", CELL, vol. 163, no. 3, 25 September 2015 (2015-09-25), pages 759 - 71
- CONG ET AL., SCIENCE, vol. 236, 1987, pages 1532 - 1539
- WARREN ET AL., CELL STEM CELL, vol. 7, no. 5, 2010, pages 618 - 30
- MANDAL PKROSSI DJ, NAT PROTOC, vol. 8, no. 3, 2013, pages 568 - 82
- "Series: Methods in Molecular Biology", vol. 1428, article "Synthetic mRNA: Production, Introduction Into Cells, and Physiological Consequences"
- "Methods in Enzymology", vol. 546, 2014, ELSEVIER, article "The use of CRISPR/Cas9, ZFNs, and TALENs in generating site-specific genome alterations. Methods Enzymol"
- CARROLL, D.: "Genome Editing with Targetable Nucleases", ANNU. REV. BIOCHEM, vol. 83, 2014, pages 409 - 39, XP055251978, DOI: 10.1146/annurev-biochem-060713-035418
- BEAUCAGEIYER, TETRAHEDRON, vol. 49, 1993, pages 1925
- LASIC, TRENDS BIOTECHNOL, vol. 16, 1998, pages 307 - 321
- DRUMMOND ET AL., PHARMACOL. REV., vol. 51, 1999, pages 691 - 743
- LASIC, TRENDS BIOTECHNOL., vol. 16, 1998, pages 307 - 321
- LASIC ET AL., FEBS LETT., vol. 312, 1992, pages 255 - 258
- N. J. CAPLEN ET AL., GENE THER, vol. 2, 1995, pages 603
- S. LI ET AL., GENE THER, vol. 4, 1997, pages 891
- FELGNER ET AL., PROC. NAT'L ACAD. SCI., vol. 84, 1987, pages 7413
- BEHR ET AL., PROC. NAT'L ACAD. SCI., vol. 86, 1989, pages 6982
- SEMPLE ET AL., NATURE BIOTECH, vol. 28, 2010, pages 172 - 176
- MORRISSEY, D V. ET AL., NAT. BIOTECHNOL., vol. 23, no. 8, 2005, pages 1003 - 1007
- GAO ET AL., BIOCHEM. BIOPHYS. RES. COMM., vol. 179, 1991, pages 280
- WOLF ET AL., BIOTECHNIQUES, vol. 23, 1997, pages 139
- KLIVANOV ET AL., FEBS LETTERS, vol. 268, no. 1, 1990, pages 235 - 237
- BLOOMFIELD, ANN. REV. BIOPHYS. BIOENG, vol. 10, 1981, pages 421 - 450
- PADDISON ET AL.: "Short hairpin RNAs (shRNAs) induce sequence-specific silencing in mammalian cells", GENES DEV, vol. 16, no. 8, 2002, pages 948 - 58, XP002204653, DOI: 10.1101/gad.981002
- CARTHEW ET AL.: "Origins and Mechanisms of miRNAs and siRNAs", CELL, vol. 136, 20 February 2009 (2009-02-20), pages 642 - 655, XP055091221, DOI: 10.1016/j.cell.2009.01.035
- HARBORTH ET AL., ANTISENSE NUCLEIC ACID DRUG DEV, vol. 13, 2003, pages 83 - 106
- CECH, ANN. REV. BIOCHEM, vol. 59, 1990, pages 543 - 568
- CECH, CURR. OPIN. STRUCT. BIOL, vol. 2, 1992, pages 605 - 609
- COUTURESTINCHOMB, TRENDS GENET, vol. 12, 1996, pages 510 - 515
- HEPELEV ET AL.: "Characterization of genome-wide enhancer-promoter interactions reveals co-expression of interacting genes and modes of higher order chromatin organization", CELL RES, vol. 22, 2012, pages 490 - 503
- ZHANG ET AL., GENOME BIOLOGY, 2008
- PHANSTIEL ET AL., BIOINFORMATICS, 2015
- ADHYA, S: "Multipartite genetic control elements: communication by DNA loop", ANNU. REV. GENET., vol. 23, 1989, pages 227 - 250
- ALLEN, B.L.TAATJES, D.J.: "The Mediator complex: a central integrator of transcription", NAT. REV. MOL. CELL BIOL., vol. 16, 2015, pages 155 - 166
- AMOUTZIAS, G.D.ROBERTSON, D.L.VAN DE PEER, Y.OLIVER, S.G.: "Choose your partners: dimerization in eukaryotic transcription factors", TRENDS BIOCHEM. SCI., vol. 33, 2008, pages 220 - 229, XP022679145, DOI: 10.1016/j.tibs.2008.02.002
- BEAGAN, J.A.DUONG, M.T.TITUS, K.R.ZHOU, L.CAO, Z.MA, J.LACHANSKI, C. VGILLIS, D.R.PHILLIPS-CREMINS, J.E.: "YY1 and CTCF orchestrate a 3-D chromatin looping switch during early neural lineage commitment", GENOME RES, 2017
- BELL, A.C.FELSENFIELD, G.: "Methylation of a CTCF-dependent boundary controls imprinted expression of the Igf2 gene", NATURE, vol. 405, 2000, pages 2 - 5
- BONEV, BCAVALLI, G: "Organization and function of the 3D genome", NAT. REV. GENET., vol. 17, 2016, pages 772 - 772
- BUECKER, CWY SOCKA, J: "Enhancers as information integration hubs in development: Lessons from genomics", TRENDS GENET, vol. 28, 2012, pages 276 - 284, XP002685092, DOI: 10.1016/J.TIG.2012.02.008
- BULGER, M.GROUDINE, M.: "Functional and mechanistic diversity of distal transcription enhancers", CELL, 2011
- CREYGHTON, M.P.CHENG, A.W.WELSTEAD, G.G.KOOISTRA, T.CAREY, B.W.STEINE, E.J.HANNA, J.LODATO, M.A.FRAMPION, G.M.SHARP, P.A. ET AL.: "Histone H3K27ac separates active from poised enhancers and predicts developmental state", PROC. NATL. ACAD. SCI. U. S. A., vol. 107, 2010, pages 21931 - 21936, XP055074651, DOI: 10.1073/pnas.1016071107
- CUDDAPAH, S.JOTHI, R.SCHONES, D.E.ROH, T.Y.CUI, K.ZHAO, K.: "Global analysis of the insulator binding protein CTCF in chromatin barrier regions reveals demarcation of active and repressive domains", GENOME RES, vol. 19, 2009, pages 24 - 32
- DEGNER, S.C.VERMA-GAUR, J.WONG, T.P.BOSSEN, C.IVERSON, G.M.TORKAMANI, A.VETTERMANN, C.LIN, Y.C.JU, ZSCHULZ, D ET AL.: "CCCTC-binding factor (CTCF) and cohesin influence the genomic architecture of the IgH locus and antisense transcription in pro-B cells", PROC. NATL. ACAD. SCI., vol. 108, 2011, pages 9566 - 9571

- DENG, W., LEE, J., WANG, H., MILLER, J., REIK, A., GREGORY, P.D., DEAN, A., BLOBEL, G.A.: "Controlling long-range genomic interactions at a native locus by targeted tethering of a looping factor", *CELL*, vol. 149, 2012, pages 1233 - 1244, XP055222117, DOI: 10.1016/j.cell.2012.03.051
- DIXON, J.R., SELVARAJ, S., YUE, F., KIM, A., LI, Y., SHEN, Y., HU, M., LIU, J.S., REN, B.: "Topological domains in mammalian genomes identified by analysis of chromatin interactions", *NATURE*, vol. 485, 2012, pages 376 - 380, XP055178389, DOI: 10.1038/nature11082
- DONOHUE, M.E., ZHANG, X., MCGINNIS, L., BIGGERS, J., LI, E., SHI, Y.: "Targeted disruption of mouse Yin Yang 1 transcription factor results in peri-implantation lethality", *MOL. CELL. BIOL.*, vol. 19, 1999, pages 7237 - 7244
- DOWEN, J.M., FAN, Z.P., HNISZ, D., REN, G., ABRAHAM, B.J., ZHANG, L., NWEINTRAUB, A., SCHUIJERS, J., LEE, T.I., ZHAO, K. ET AL.: "Control of Cell Identity Genes Occurs in Insulated Neighborhoods in Mammalian Chromosomes", *CELL*, vol. 159, 2014, pages 374 - 387, XP029073420, DOI: 10.1016/j.cell.2014.09.030
- ERB, M.A., SCOTT, T.G., LI, B.E., XIE, H., PAULK, J., SEO, H.-S., SOUZA, A., ROBERTS, J.M., DASTJERDI, S., BUCKLEY, D.L. ET AL.: "Transcription control by the ENL YEATS domain in acute leukaemia", *NATURE*, vol. 543, 2017, pages 270 - 274, XP055935703, DOI: 10.1038/nature21688
- FRASER, J., WILLIAMSON, I., BICKMORE, W., ADOSTIE, J.: "An Overview of Genome Organization and How We Got There: from FISH to Hi-C", *MICROBIOL. MOL. BIOL. REV.*, vol. 79, 2015, pages 347 - 372
- FULLWOOD, M., J. LIU, M.H., PAN, Y.F., LIU, J., XU, H., MOHAMED, Y., BINORLOV, Y.L., VELKOV, S., HO, A., MEI, P.H. ET AL.: "An oestrogen-receptor-alpha-bound human chromatin interactome", *NATURE*, vol. 462, 2009, pages 58 - 64, XP055015076, DOI: 10.1038/nature08497
- GABRIELE, M., VULTO-VAN SILFHOUT, A.T., GERMAIN, P.-L., VITRILOLO, A., KUMAR, R., DOUGLAS, E., HAAN, E., KOSAKI, K., TAKENOUCHI, T., RAUCH, A. ET AL.: "YY1 Haploinsufficiency Causes an Intellectual Disability Syndrome Featuring Transcriptional and Chromatin Dysfunction", *AM. J. HUM. GENET.*, vol. 100, 2017, pages 907 - 925, XP085053327, DOI: 10.1016/j.ajhg.2017.05.006
- GIBCUS, J.H., DEKKER, J.: "The hierarchy of the 3D genome", *MOL. CELL*, vol. 49, 2013, pages 773 - 782, XP028590130, DOI: 10.1016/j.molcel.2013.02.011
- GORDON, S., AKOPYAN, G., GARBAN, H., BONAVIDA, B.: "Transcription factor YY1: structure, function, and therapeutic implications in cancer biology", *ONCOGENE*, vol. 25, 2006, pages 1125 - 1142, XP037743480, DOI: 10.1038/sj.onc.1209080
- GORKIN, D., U. LEUNG, D., REN, B.: "The 3D Genome in Transcriptional Regulation and Pluripotency", *CELL STEM CELL*, vol. 14, 2014, pages 762 - 775
- GUO, C., YOON, H.S., FRANKLIN, A., JAIN, S., EBERT, A., CHENG, H.-L., HANSEN, E., DESPO, O., BOSSEN, C., VETTERMANN, C. ET AL.: "CTCF-binding elements mediate control of V(D)J recombination", *NATURE*, vol. 477, 2011, pages 424 - 430, XP055445637, DOI: 10.1038/nature10495
- GUO, Y., XU, Q., CANZIO, D., SHOU, J., LI, J., GORKIN, D., U. JUNG, I., WU, H., ZHAI, Y., TANG, Y. ET AL.: "CRISPR Inversion of CTCF Sites Alters Genome Topology and Enhancer/Promoter Function", *CELL*, vol. 162, 2015, pages 900 - 910, XP055365405, DOI: 10.1016/j.cell.2015.07.038
- HARIHARAN, N., KELLEY, D.E., PERRY, R.P.: "Delta, a transcription factor that binds to downstream elements in several polymerase II promoters, is a functionally versatile zinc finger protein", *PROC. NATL. ACAD. SCI. U. S. A.*, vol. 88, 1991, pages 9799 - 9803
- HEARD, E., BICKMORE, W.: "The ins and outs of gene regulation and chromosome territory organisation", *CURR. OPIN. CELL BIOL.*, vol. 19, 2007, pages 311 - 316, XP022116696
- HEATH, H., RIBEIRO DE ALMEIDA, C., SLEUTELS, F., DINGJAN, G., VAN DE NOBEL, S., JONKERS, I., LING, K.-W., GRIBNAU, J., RENKAWITZ, R., GROSVELD, F.: "CTCF regulates cell cycle progression of alphabeta T cells in the thymus", *EMBO J.*, vol. 27, 2008, pages 2839 - 2850
- HNISZ, D., DAY, D.S., YOUNG, R.A.: "Insulated Neighborhoods: Structural and Functional Units of Mammalian Gene Control", *CELL*, vol. 167, 2016, pages 1188 - 1200, XP029812213, DOI: 10.1016/j.cell.2016.10.024
- HNISZ, D., WEINTRAUB, A.S., DAY, D.S., VALTON, A.-L., BAK, R., O.L.I., C.H., GOLDMANN, J., LAJOIE, B., R.FAN, Z.P., SIGOVA, A.A. ET AL.: "Activation of proto-oncogenes by disruption of chromosome neighborhoods", *SCIENCE*, vol. 80, no. 351, 2016, pages 1454 - 1458
- HUANG, H., SEO, H., ZHANG, T., WANG, Y., JIANG, B., LI, Q., BUCKLEY, D., L. NABET, B., ROBERTS, J.M., PAULK, J. ET AL.: "MELK IS NOT NECESSARY FOR THE PROLIFERATION OF BASAL-LIKE BREAST CANCER CELLS", 2017, pages 1 - 29
- HWANG, S.S., KIM, Y.U., LEE, S., JANG, S.W., KIM, M.K., KOH, B.H., LEE, W., KIM, J., SOUABNI, A., BUSSLINGER, M. ET AL.: "Transcription factor YY1 is essential for regulation of the Th2 cytokine locus and for Th2 cell differentiation", *PROC. NATL. ACAD. SCI.*, vol. 110, 2013, pages 276 - 281
- JERONIMO, C., LANGELIER, M.F., BATAILLE, A.R., PASCAL, J.M., PUGH, B.F., ROBERT, F.: "Tail and Kinase Modules Differently Regulate Core Mediator Recruitment and Function In Vivo. Mol", *CELL*, vol. 64, 2016, pages 455 - 466
- Ji, X., DADON, D.B., ABRAHAM, B.J., IHN, T., JAENISCH, R., BRADNER, J.E., YOUNG, R.A.: "Chromatin proteomic profiling reveals novel proteins associated with histone-marked genomic regions", *PROC. NATL. ACAD. SCI.*, vol. 112, 2015, pages 3841 - 3846
- Ji, X., DADON, D., POWELL, B., FAN, Z.P., BORGES-RIVERA, D., SHACHAR, S., WEINTRAUB, A.S., HNISZ, D., PEGORARO, G., LEE, T.I. ET AL.: "3D Chromosome Regulatory Landscape of Human Pluripotent Cells", *CELL STEM CELL*, vol. 18, 2016, pages 1 - 14
- KAGEY, M.H., NEWMAN, J.J., BILODEAU, S., ZHAN, Y., ORLANDO, D., AVAN BERKUM, N.L., EBMEIER, C.C., GOOSSENS, J., RAHL, P.B., LEVINE, S.S. ET AL.: "Mediator and cohesin connect gene expression and chromatin architecture", *NATURE*, vol. 467, 2010, pages 430 - 435, XP055307052, DOI: 10.1038/nature09380
- KIM, T.H., ABDULLAEV, Z.K., SMITH, A.D., CHING, K.A., LOUKINOV, D.I., GREEN, R.D., D. ZHANG, M.Q., LOBANENKOV, V. V., REN, B.: "Analysis of the Vertebrate Insulator Protein CTCF-Binding Sites in the Human Genome", *CELL*, vol. 128, 2007, pages 1231 - 1245, XP002592949, DOI: 10.1016/j.cell.2006.12.048
- KLENOVA, E.M., NICOLAS, R.H., PATERSON, H.F., CARNE, A.F., HEATH, C.M., GOODWIN, G.H., NEIMAN, P.E., LOBANENKOV, V. V.: "CTCF, a conserved nuclear factor required for optimal transcriptional activity of the chicken c-myc gene, is an 11-Zn-finger protein differentially expressed in multiple forms", *MOL. CELL. BIOL.*, vol. 13, 1993, pages 7612 - 7624, XP000882021
- DE LAAT, W., DUBOULE, D.: "Topology of mammalian developmental enhancers and their regulatory landscapes", *NATURE*, vol. 502, 2013, pages 499 - 506
- LAMB, P., MCKNIGHT, S.L.: "Diversity and specificity in transcriptional regulation: the benefits of heterotypic dimerization", *TRENDS BIOCHEM. SCI.*, vol. 16, 1991, pages 417 - 422, XP025864822, DOI: 10.1016/0968-0004(91)90167-T
- LEVINE, M., CATTOGLIO, C., TJIAN, R.: "Looping back to leap forward: Transcription enters a new era", *CELL*, vol. 157, 2014, pages 13 - 25, XP028601882, DOI: 10.1016/j.cell.2014.02.009
- LIU, H., SCHMIDT-SUPPRIAN, M., SHI, Y., HOBEIKA, E., BARTENEVA, N., JUMAA, H., PELANDA, R., RETH, M., SKOK, J., RAJEWSKY, K. ET AL.: "YIN YANG 1 IS A CRITICAL REGULATOR OF B-CELL DEVELOPMENT", 2007, pages 1179 - 1189
- LOPEZ-PERROTE, A., ALATWI, H.E., TORREIRA, E., ISMAIL, A., AYORA, S., DOWNS, J.A., LLORCA, O.: "Structure of Yin Yang 1 oligomers that cooperate with RuvBL1-RuvBL2 ATPases", *J. BIOL. CHEM.*, vol. 289, 2014, pages 22614 - 22629
- LUPIANEZ, D.G., KRAFT, K., HEINRICH, V., KRAWITZ, P., BRANCATI, F., KLOPOCKI, E., HORN, D., KAYSERILI, H., OPITZ, J.M., LAXOVA, R. ET AL.: "Disruptions of Topological Chromatin Domains Cause Pathogenic Rewiring of Gene-Enhancer Interactions", *CELL*, 2015, pages 1 - 14
- MALIK, S., ROEDER, R.G.: "The metazoan Mediator co-activator complex as an integrative hub for transcriptional regulation", *NAT. REV. GENET.*, vol. 11, 2010, pages 761 - 772
- MATTHEWS, K.S.: "DNA looping", *MICROBIOL. REV.*, vol. 56, 1992, pages 123 - 136
- MELE, M., FERREIRA, P.G., REVERTER, F., DELUCA, D.S., MONLONG, J., SAMMETH, M., YOUNG, T.R., GOLDMANN, J.M., PERVOUCHINE, D.D., SULLIVAN, T.J. ET AL.: "The human transcriptome across tissues and individuals", *SCIENCE*, vol. 80, no. 348, 2015, pages 660 - 665
- MERKENSCHLAGER, M., NORA, E.P.: "CTCF and Cohesin in Genome Folding and Transcriptional Gene Regulation", *ANNU. REV. GENOMICS HUM. GENET.*, vol. 17, 2016, pages 1 - 27
- MUERDTER, F., STARK, A.: "Gene Regulation: Activation through Space", *CURR. BIOL.*, vol. 26, 2016, pages R895 - R898, XP029762771, DOI: 10.1016/j.cub.2016.08.031
- MUMBACH, M.R., RUBIN, A.J., FLYNN, R.A., DAI, C., KHAVARI, P.A., GREENLEAF, W.J., CHANG, H.Y.: "HiChIP: efficient and sensitive analysis of protein-directed genome architecture", *NAT. METHODS*, vol. 13, 2016, pages 919 - 922
- NARENDRA, V., ROCHA, P.P., AN, D., RAVIRAM, R., SKOK, J.A., MAZZONI, E.O., REINBERG, D.: "CTCF ESTABLISHES DISCRETE FUNCTIONAL CHROMATIN DOMAINS AT THE HOX CLUSTERS DURING DIFFERENTIATION", vol. 347, 2015, pages 1017 - 1022

- NORA, E.P.LAJOIE, B.R.SCHULZ, E.G.GIORGETTI, L.OKAMOTO, I.SERVANT, N.PIOLOT, T.VAN BERKUM, N.L.MEISIG, J.SEDAT, J. ET AL.: "Spatial partitioning of the regulatory landscape of the X-inactivation centre", NATURE, vol. 485, 2012, pages 381 - 385
- NORA, E.P.GOLOBORODKO, A.VALTON, A.-L.GIBBUS, J.H.UEBERSOHN, A.ABDENNUR, N.DEKKER, J.MIRNY, L.A.BRUNEAU, B.G.: "Targeted Degradation of CTCF Decouples Local Insulation of Chromosome Domains from Genomic Compartmentalization", CELL, vol. 169, 2017, pages 930 - 944
- OHLSSON, R.RENKAWITZ, R.LOBANENKOV, V.: "CTCF is a uniquely versatile transcription regulator linked to epigenetics and disease", TRENDS GENET, vol. 17, 2001, pages 520 - 527, XP004303293, DOI: 10.1016/S0168-9525(01)02366-6
- ONG, C.CORCES, V.: "Enhancer function: new insights into the regulation of tissue-specific gene expression", NAT. REV. GENET., vol. 12, 2011, pages 283 - 293, XP055253004, DOI: 10.1038/nrg2957
- PARK, K.ATCHISON, M.L.: "Isolation of a candidate repressor/activator, NF-E1 (YY1, d), that binds to the immunoglobulin k 3' enhancer and the immunoglobulin heavy-chain mE1 site", PROC. NATL. ACAD. SCI., vol. 88, 1991, pages 9804 - 9808
- PETRENKO, N.JIN, Y.WONG, K.H.STRUHL, K.: "Mediator Undergoes a Compositional Change during Transcriptional Activation", MOL. CELL, vol. 64, 2016, pages 443 - 454, XP029802800, DOI: 10.1016/j.molcel.2016.09.015
- PHILLIPS, J.E.CORCES, V.G.: "CTCF: master weaver of the genome", CELL, vol. 137, 2009, pages 1194 - 1211
- POMBO, A.DILLON, N.: "Three-dimensional genome architecture: players and mechanisms", NAT. REV. MOL. CELL BIOL., 2015, pages 12
- RAO, S.S.P.HUNTLEY, M.H.DURAND, N.C.STAMENOVA, E.K.BOCHKOV, I.D.ROBINSON, J.T.SANBORN, A.L.MACHOL, I.OMER, A.D.LANDER, E. S ET AL.: "A 3D Map of the Human Genome at Kilobase Resolution Reveals Principles of Chromatin Looping", CELL, 2014, pages 1 - 16
- REN, B.YUE, F.: "Transcriptional enhancers: Bridging the genome and phenotype", COLD SPRING HARBOR SYMPOSIA ON QUANTITATIVE BIOLOGY, 2016, pages 17 - 26
- SALDANA-MEYER, R.GONZALEZ-BUENDIA, E.GUERRERO, G.NARENDRA, V.BONASIO, R.RECILLAS-TARGA, F.REINBERG, D.: "CTCF regulates the human p53 gene through direct interaction with its natural antisense transcript, Wrap53", GENES DEV, vol. 28, 2014, pages 723 - 734
- SCHLEIF, R.: "DNA looping", ANNU. REV. BIOCHEM., vol. 61, 1992, pages 199 - 223
- SCHMIDT, D.SCHWALIE, P.C.ROSS-INNES, C.S.HURTADO, A.BROWN, G.D.CARRROLL, J.S.FLICEK, P.ODOM, D.T.: "A CTCF-independent role for cohesin in tissue-specific transcription", GENOME RES, vol. 20, 2010, pages 578 - 588
- SHI, Y.SETO, E.CHANG, L.S.SHENK, T.: "Transcriptional repression by YY1, a human GLI-Kruppel-related protein, and relief of repression by adenovirus E1A protein", CELL, vol. 67, 1991, pages 377 - 388, XP024244830, DOI: 10.1016/0092-8674(91)90189-6
- SHI, Y.LEE, J.S.GALVIN, K.M.: "Everything you have ever wanted to know about Yin Yang 1", BIOCHIM. BIOPHYS. ACTA - REV. CANCER, 1997, pages 1332
- SHORE, D.LANGOWSKI, J.BALDWIN, R.L.: "DNA flexibility studied by covalent closure of short fragments into circles", PROC. NATL. ACAD. SCI. U. S. A., vol. 78, 1981, pages 4833 - 4837, XP055278377
- SIGOVA, A.A.ABRAHAM, B.J.JI, X.MOLINIE, B.HANNETT, N.M.GUO, Y.E.JANGI, M.GIALLOURAKIS, C.C.SHARP, P. A.YOUNG, R.A.: "Transcription factor trapping by RNA in gene regulatory elements", SCIENCE, vol. 80, no. 350, 2015, pages 978 - 981
- SPITZ, F.: "Gene regulation at a distance: From remote enhancers to 3D regulatory ensembles", SEMIN. CELL DEV. BIOL., vol. 57, 2016, pages 57 - 67, XP029675189, DOI: 10.1016/j.semcdb.2016.06.017
- SPLINTER, E.HEATH, H.KOOREN, J.PALSTRA, R.-J.KLOUS, P.GROSVELD, F.GALJART, N.DE LAAT, W.: "CTCF mediates long-range chromatin looping and local histone modification in the beta-globin locus", GENES DEV, 2006, pages 2349 - 2354
- TANG, Z.LUO, O.J.LI, X.ZHENG, M.ZHU, J.J.SZALAJ, P.TRZASKOMA, P.MAGALSKA, A.WLODARCZYK, J.RUSZCZYCKI, B. ET AL.: "CTCF-Mediated Human 3D Genome Architecture Reveals Chromatin Topology for Transcription", CELL, vol. 163, 2015, pages 1611 - 1627, XP029360511, DOI: 10.1016/j.cell.2015.11.024
- THOMAS, M.J.SETO, E.: "Unlocking the mechanisms of transcription factor YY1: Are chromatin modifying enzymes the key?", GENE, vol. 236, 1999, pages 197 - 208, XP004178056, DOI: 10.1016/S0378-1119(99)00261-9
- WANG, T.BIRSOY, K.HUGHES, N.W.KRUPCZAK, K.M.POST, Y.WEI, J.J.LANDER, E.S.SABATINI, D.M.: "Identification and characterization of essential genes in the human genome", SCIENCE, vol. 80, no. 350, 2015, pages 1096 - 1101
- WEIRAUCH, M.T.HUGHES, T.R.: "A Handbook of Transcription Factors, Subcellular Biochemistry", 2011, article "A catalogue of eukaryotic transcription factor types, their evolutionary origin, and species distribution", pages: 25 - 73
- WENDT, K.S.YOSHIDA, K.ITOH, T.BANDO, M.KOCH, B.SCHIRGHUBER, E.TSUTSUMI, S.NAGAE, G.ISHIHARA, K.MISHIRO, T. ET AL.: "Cohesin mediates transcriptional insulation by CCTC-binding factor", NATURE, vol. 451, 2008, pages 796 - 801
- WINTER, G.E.BUCKLEY, D.L.PAULK, J.ROBERTS, J.M.SOUZA, A.DHE-PAGANON, S.BRADNER, J.E.: "Phthalimide conjugation as a strategy for in vivo target protein degradation", SCIENCE, vol. 348, 2015, pages 1376 - 1381, XP055328122, DOI: 10.1126/science.aab1433
- YIN, Y.MORGUNOVA, E.JOLMA, A.KAASINEN, E.SAHU, B.KHUND-SAYEED, S.DAS, P.K.KIVIOJA, T.DAVE, K.ZHONG, F. ET AL.: "Impact of cytosine methylation on DNA binding specificities of human transcription factors", SCIENCE, vol. 80, no. 356, 2017, pages eaaj2239
- ZHANG, Q.STOVALL, D.B.INOUE, K.SUI, G., THE ONCOGENIC ROLE OF YIN YANG, 2011, pages 1

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